DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125377/S-096

ACCELERATED APPROVAL

Bristol-Myers Squibb Company
Attention: Noemi Guma, Ph.D.
Director, Global Regulatory, Safety & Biometrics
P.O. Box 4000
Princeton, NJ 08543

Dear Dr. Guma:

Please refer to your supplemental Biologics License Application (sBLA) dated January 10, 2018, received January 10, 2018, submitted under section 351(a) of the Public Health Service Act for YERVOY (ipilimumab) injection, 50 mg/10 mL and 200 mg/40 mL.

This Prior Approval supplemental biologics application provides for a new indication for YERVOY, in combination with nivolumab, is indicated for the treatment of adults and pediatric patients 12 years and older with microsatellite instability-high (MSI H) or DNA mismatch repair deficient (dMMR), metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.40), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical to the enclosed labeling (text for the prescribing information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated July 10, 2018. This requirement, along with required completion dates, is listed below.

This postmarketing clinical trial is subject to the reporting requirements of 21 CFR 601.70:

3450-1 Submit the final report, including datasets, from a randomized trial conducted to verify and describe the clinical benefit of ipilimumab, administered in combination with nivolumab, in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer. The trial will be designed to demonstrate a clinically meaningful improvement in progression-free survival in patients randomized to receive ipilimumab and nivolumab as compared to patients randomized to receive nivolumab alone. In addition, the trial should evaluate for differences in overall survival between arms based on a pre-specified analysis. The analysis plan should describe the power for the overall survival analysis, as well as all assumptions made in determining the power.

Final Protocol Submission:	12/2018
Trial Completion:	12/2023
Final Report Submission:	07/2024

Submit clinical protocols to your IND 119381 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this indication because necessary studies are impossible or highly impracticable since the disease/condition does not exist in children.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3450-2 Submit the final report, including datasets, from trials conducted to describe the clinical benefit of ipilimumab, administered in combination with nivolumab, in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer. This report is to include data on 119 patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer enrolled in Study CA209142 whose preliminary results are described in current labeling and on the 82-patient subset of these 119 patients who experienced disease progression on 5FU, oxaliplatin, and irinotecan. The final report will provide updated data on all responding patients who will be followed for at least 12 months from the onset of response.

The timetable you submitted on July 10, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2019

3450-3 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry-based in vitro diagnostic device that is essential to the safe and effective use of ipilimumab for patients with tumors that are mismatch repair deficient.

The timetable you submitted on July 10, 2018, states that you will support the submission of a Premarket Approval (PMA) Application to FDA/CDRH according to the following schedule:

Final Report Submission: 07/2024

3450-4 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of ipilimumab for patients with tumors that are microsatellite instability-high.

The timetable you submitted on July 10, 2018, states that you will support the submission of a Premarket Approval (PMA) Application to FDA/CDRH according to the following schedule:

Final Report Submission: 07/2024

Submit clinical protocols to your IND 119381 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved prescribing information (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Meredith Libeg, Senior Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICIA KEEGAN
07/10/2018